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Prostaglandins inhibit lipoprotein lipase gene expression in macrophages

J. B. DESANCTIS,* L. VARESIO† & D. RADZIOCH‡ *Institute of Immunology, Central University of Venezuela, Caracas, Sabana Grande, Venezuela, †Frederick Cancer Research Facility, National Cancer Institute, Frederick, Maryland, U.S.A. and ‡McGill University, McGill Centre for the Study of Host Resistance, Montreal General Hospital, Quebec, Canada

SUMMARY

In the present investigation of the effects of prostaglandin E_2 (PGE_2) on lipoprotein lipase (LPL) gene expression in macrophages, we observed that treatment of macrophages with PGE_2 increased the levels of adenosine 3′,5′-cyclic monophosphate (cAMP), while the addition of exogenous 5-bromo-cAMP to macrophage cultures resulted in down-regulation of LPL expression. Using indomethacin (INDO), an inhibitor of cyclo-oxygenase and prostaglandins production, we determined that PGE_2 acts as a feedback inhibitor of LPL expression. We found that inhibited secretion of LPL protein in lipopolysaccharide (LPS)-treated macrophages could be restored to control levels by the addition of INDO to the medium. In contrast, INDO did not reverse the inhibition of LPL mRNA induced by LPS. Overall, our results have demonstrated that PGE_2 is a potent inhibitor of LPL gene expression and indicated that its action may play an important physiological role in the regulation of LPL gene expression during bacterial infections.

INTRODUCTION

Lipoprotein lipase (LPL) (EC 3.1.1.34) is the key enzyme in the hydrolysis of triglyceride-rich lipoprotein (QM, VLDL) and plays an important role in the metabolism of other lipoproteins, including IDL, LDL and HDL.[1] LPL regulates the uptake of triacylglycerol fatty acids from the circulation, acting at the level of the vascular endothelium. Endothelial cells acquire LPL from other cells such as adipose tissue, and LPL has also been found in macrophages.[2–5]

Changes in the levels of LPL secretion can be associated with different diseases of lipid and lipoprotein metabolism.[5] For example, a massive secretion of LPL by macrophages is thought to be responsible for the generation of metabolites that cause the development of atherosclerotic lesions.[3] Diminished LPL activity has been observed in animals infected with Gram-negative bacteria,[5] and it has been observed that the injection of lipopolysaccharide (LPS) into experimental animals causes massive hypertriglyceridaemia while it decreases the amount of membrane-bound LPL.[6]

Inflammatory macrophages and monocytes secrete considerable amounts of prostaglandins, the oxygenated metabolites of essential polysaturated fatty acids.[7,8] The effect of prostaglandin E_2 (PGE_2) on LPL gene expression in macrophages has not been described. In this report, we examine the effects of prostaglandins on the regulation of LPL gene expression in macrophages. Overall, our results show the mechanism responsible for the down-regulation of LPL activity and indicate the importance of arachidonic acid metabolites in the regulation of this enzyme.

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Abbreviations: cAMP, adenosine 3′,5′-cyclic monophosphate; INDO, indomethacin; LPL, lipoprotein lipase; LPS, lipopolysaccharide; PGE_2, prostaglandins.

Correspondence: Dr D. Radzioch, McGill Centre for the Study of Host Resistance, MGH, Room LH 11-218, 1650 Cedar Ave, Montreal, Quebec, H3G 1A4, Canada.

MATERIALS AND METHODS

Reagents

The following reagents were used: fetal bovine serum (FBS) from Hyclone Laboratories Inc. (Logan, UT); LPS, indomethacin (INDO), PGE_2, 8 bromo-adenosine 3′,5′-cyclic monophosphate (cAMP), o-phenyldiamine and hydrogen peroxide from Sigma Chemical Co. (St Louis, MO).

Animals

C67BL/6 strain mice were obtained from the Animal Production Facility, National Cancer Institute, Frederick Cancer Research Facility, Frederick, MD. The mice were used between 8 and 12 weeks of age.

Macrophages

Mice were injected intraperitoneally with thioglycollate medium (BBL Microbiology Systems, Cockeysville, MD), and peritoneal exudate cells were harvested 4 days later by washing the peritoneal cavity with Eagle's minimum essential medium (Gibco Laboratories, Grand Island, NY). The peritoneal exudate cells were washed three times with Hanks' balanced salt solution (HBSS; Gibco) and the macrophages were purified by adherence to plastic. Viability, determined by trypan blue exclusion, was greater than 95%. Briefly, 2×10^7 macrophages were plated on 15-cm Lux plates (Miles Scientific, Napersville, IL). Ninety-five per cent of adherent cells were macrophages. After 2 hr of adherence, macrophage monolayers were washed with HBSS, and cultured in RPMI-1640 medium (Gibco-BRL,

Grand Island, NY) containing 10% FBS with the activating agents, as described in the Results.

RNA extraction

Macrophages were solubilized with guanidine isothiocyanate solution and total RNA was purified by centrifugation through a CsCl cushion according to the method of Chirgwin *et al.*[9] The purified RNA was dissolved in 10 mM Tris-HCl, pH 7·0, containing 1 μg/ml proteinase K, aliquoted and stored at $-80°$. The yield of total RNA was approximately 30 μg per 10^7 macrophages.

Northern blot analysis

Twenty micrograms of purified RNA was separated in 1·2% agarose gels containing 2·2 M formaldehyde. After electrophoresis, the gel was rinsed with water, treated briefly with 50 mM NaOH, and blotted onto a Nytran membrane (Schleicher & Schuell, Keene, NH). The RNA were cross-linked to the membrane by using UV irradiation and incubated overnight at 42° in Hybridisol I hybridization solution (Oncor, Gaithersburg, MD; buffer containing 1 × Denhard's solution, 50% formamide, 5 × SSC, 50 mM NaH_2PO_4, pH 6·5). The mRNA levels were analysed by hybridization of Northern blots with ^{32}P-labelled probes. Two oligonucleotide primers spanning bases 255–287 and 1127–1148 of the LPL cDNA were used to amplify by PCR reaction a 893-bp region of LPL cDNA using a murine macrophage cDNA template. The LPL cDNA probe was subsequently purified on a low melting agarose gel, subcloned in pGEM3 vector and sequenced. β-Actin probe was purchased from Oncor. Purified DNA inserts were labelled with ^{32}P-dCTP (Amersham Corp., Arlington Heights, IL) by random priming. Specific activity of the probes was 5×10^8 c.p.m./μg of DNA. After hybridization blots were washed three times in 2 × SSC/0·1% SDS for 15 min at room temperature and then washed twice in 0·1% SDS/0·1% SDS for 15 min at 55°. Hybridization was detected by autoradiography (1–3 days exposure) with Kodak X-Omat-AR film (Rochester, NY).

Determination of LPL activity

LPL activity was determined using a stable substrate emulsion.[10] Briefly, medium from each experimental sample (100 μl) was added to 100 μl of substrate containing glycerol tri[9,10 (n)-^{3}H]-oleate (New England Nuclear, Boston, MA), 1 mg triolein, 2 mg of bovine serum albumin (fatty acid free), 0·12 mg lecithin, 16–20% of heat-inactivated human or bovine serum and 16% (v/v) glycerol in 0·2 M Tris-HCl (pH 8·0). The substrate mixture was incubated for 60 min at 37°. The specific activity of the substrate was 100 d.p.m. per nmol of fatty acid. One unit of enzyme activity was defined as the release of 1 nmol fatty acid (FA)/min. Each experimental point was measured in quadruplicate and expressed in nmoles FA/ml/min.

Determination of LPL immunoreactive mass

LPL immunoreactive mass was measured by ELISA using affinity-purified antibodies specific for LPL using a technique we have described in detail previously.[11] Briefly, 1 μg/well of an affinity-purified murine antibody against bovine LPL was absorbed to titre plates (Immulon II; Dynatech, Alexandria, VA, or Costar, Cambridge, MA), and different dilutions of the sample (in PBS) or murine LPL standards were added and incubated overnight. The wells were then washed extensively with PBS containing 0·05% Tween 20 and affinity-purified rabbit antibody anti-murine LPL was added. Anti-rabbit IgG-peroxidase was added to the wells, and incubated for 3 hr. The peroxidase reaction was developed by adding peroxidase substrate (0·3 mg/ml o-phenylenediamine, 0·012% hydrogen peroxide in 0·1 M citrate, pH 4·5). The reaction was stopped with 25 μl of 4 M sulphuric acid and was read in an ELISA plate reader (Dynatech).

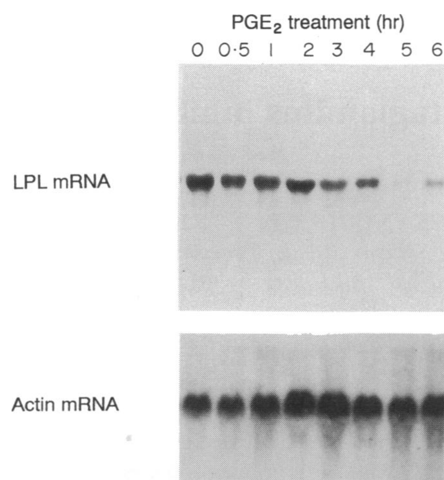

Figure 1. Inhibition of macrophage LPL mRNA expression by PGE_2. Peritoneal macrophages (10^6 cells/ml) were cultured for 6 hr in medium alone (0) or in medium containing 35 ng/ml of PGE_2 for 0·5, 1, 2, 3, 4, 5 or 6 hr, as indicated. All experimental groups were harvested at the same time. Total RNA were extracted and analysed by Northern blots for LPL mRNA and actin mRNA expression.

PGE_2 determination

2×10^6 macrophages were exposed to 1 μg/ml of LPS for 3, 6, 12 or 18 hr. The PGE_2 release in culture supernatants was determined by radioimmunoassay (RIA) with a commercially available kit (New England Nuclear).

cAMP determination

10^6 macrophages were exposed to 100 nM of PGE_2 for 5 min, 15 min, 30 min, 1 hr, 3 hr or 6 hr. The levels of secreted cAMP were measured by RIA with a commercially available kit (New England Nuclear).

RESULTS

The effects of prostaglandins on LPL mRNA (3·6 kb) expression in macrophages were investigated. Peritoneal macrophages were treated with 35 ng/ml(100 nM) PGE_2 for 0·5–6 hr and the levels of LPL mRNA expression were measured by Northern blot analysis. As shown in Fig. 1, the addition of PGE_2 inhibited LPL mRNA expression by macrophages in culture. Small but significant inhibitory effects could be observed as early as 0·5 hr and reached a maximum level at about 5 hr following treatment. The inhibition of LPL mRNA expression was not due to an overall inhibition of mRNA synthesis, since actin mRNA levels were not affected by PGE_2.

As shown in Fig. 2, the marked inhibition of LPL mRNA expression correlated with inhibition of secretion (Fig. 2a) and activity of LPL (Fig. 2b) in macrophages treated with PGE_2.

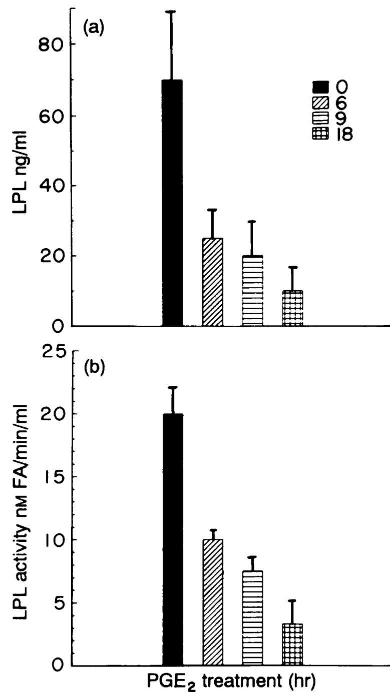

Figure 2. Inhibition of macrophage LPL mass and activity by PGE_2. Peritoneal macrophages (10^6 cells/ml) were treated with 35 ng/ml (100 nM) PGE_2 for 0, 6, 9 or 18 hr, as indicated. All supernatants were harvested following the same culture period of 18 hr and analysed for LPL protein content and activity, as described in the Materials and Methods. Results represent the means ± SEM of five triplicate determinations.

These results demonstrated that PGE_2 could inhibit both LPL mRNA expression and protein secretion.

It has been shown that PGE_2 can activate adenylate cyclase and augment cAMP levels. To investigate the potential involvement of cAMP in the down-regulation of LPL mRNA, we tested cAMP secretion by macrophages treated with 35 ng/ml of PGE_2.

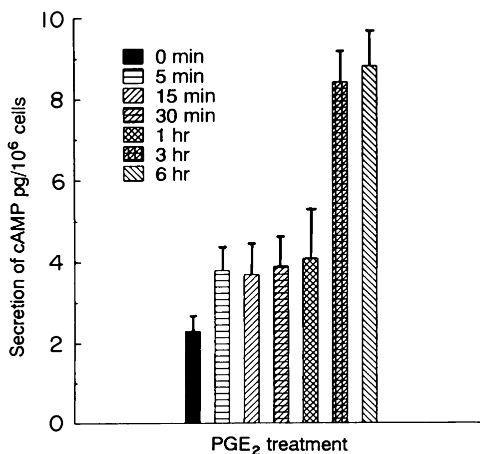

Figure 3. Macrophage secretion of cAMP in response to PGE_2 treatment. 10^6 peritoneal macrophages were exposed to 35 ng/ml of PGE_2 for 5 min, 15 min, 30 min, 1 hr, 3 hr or 6 hr. All supernatants were harvested at the same time and the levels of secreted cAMP were measured by RIA. Results represent the means ± SEM of three triplicate determinations.

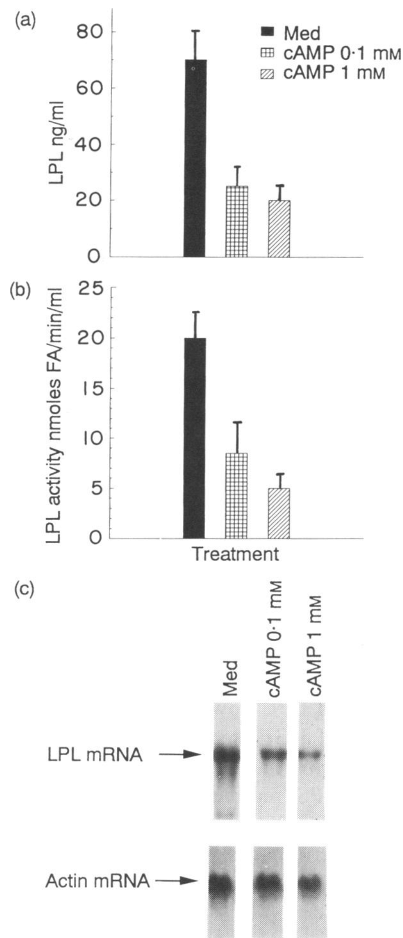

Figure 4. Inhibition of macrophage LPL mRNA expression and LPL protein secretion by cAMP. Peritoneal macrophages (10^6 cells/ml) were cultured for 9 hr in medium alone (Med) or in medium containing 100 μM 8-bromo-cAMP or 1 mM 8-bromo-cAMP. All supernatants were harvested simultaneously and analysed for LPL protein content (a) and activity (b). Results represent the means ± SEM of five triplicate determinations. Total RNA were extracted and analysed by Northern blot for LPL mRNA and actin mRNA expression (c).

As shown in Fig. 3, treatment of macrophages with PGE_2 for 3 hr resulted in a threefold increase in cAMP secretion. Treatment with PGE_2 for 6 hr did not further augment cAMP levels (Fig. 3), which returned to baseline level by 18 hr (data not shown). We subsequently tested whether or not treatment with cAMP would modulate LPL gene expression. As shown in Fig. 4a, treatment of macrophages with 8-bromo-cAMP caused an approximate three- to fourfold decrease in the secretion of LPL protein by the macrophages. As shown in Fig. 4b, LPL enzymatic activity was inhibited three- to fourfold as well. Strong inhibition of LPL secretion and activity correlated with inhibition of LPL mRNA expression in macrophages treated with 8-bromo-cAMP (Fig. 4c). These results demonstrated that PGE_2 and cAMP could inhibit LPL mRNA and protein expression and suggested that an increase in cAMP could mediate the inhibitory effects of PGE_2.

Prostaglandins are secreted by macrophages in response to a variety of activating agents, including LPS. Since it has been shown that treatment of macrophages with LPS inhibits LPL

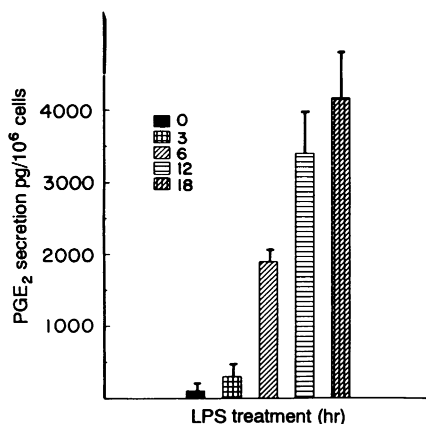

Figure 5. PGE_2 secretion by macrophages in response to LPS treatment. All experimental groups of macrophages were cultured for 18 hr. 10^6 macrophages were exposed to 1 μg/ml of LPS for 0, 3, 6, 12 or 18 hr. All supernatants were harvested following the same culture period of 18 hr and PGE_2 release in culture supernatants was determined by RIA, as described in the Materials and Methods. Results represent the means ± SEM of three triplicate determinations.

gene expression,[12,13] we investigated whether LPS-induced PGE_2 could be involved in LPL down-regulation. Firstly, we monitored the kinetics of PGE_2 secretion by macrophages treated with LPS. As shown in Fig. 5, increasing amounts of PGE_2 were secreted following LPS treatment. To assess whether or not the inhibitory effects of LPS on LPL gene expression involved prostaglandins, macrophages were cultured in medium alone

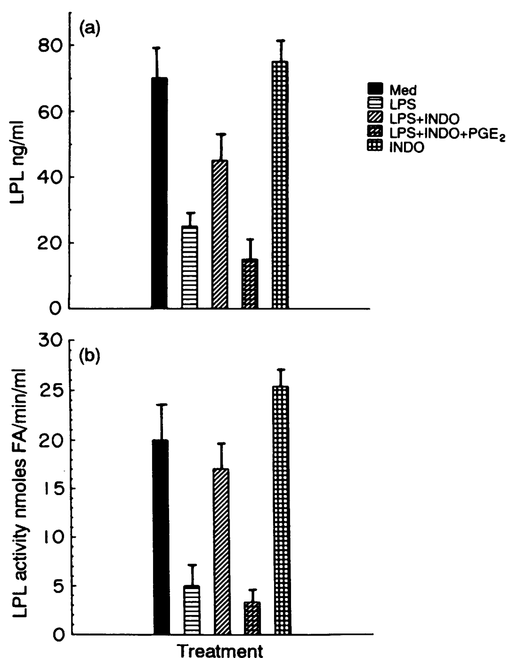

Figure 6. Effect of INDO on macrophage LPL secretion. Peritoneal macrophages (10^6 cells/ml) were cultured for 18 hr in medium alone (Med) or in medium containing 1 μg/ml of LPS, 100 nM INDO, LPS plus INDO or LPS plus INDO plus 35 ng/ml of PGE_2. All supernatants were harvested at the same time and analysed for LPL protein content (a) and activity (b). Results represent the means ± SEM of five triplicate deteminations.

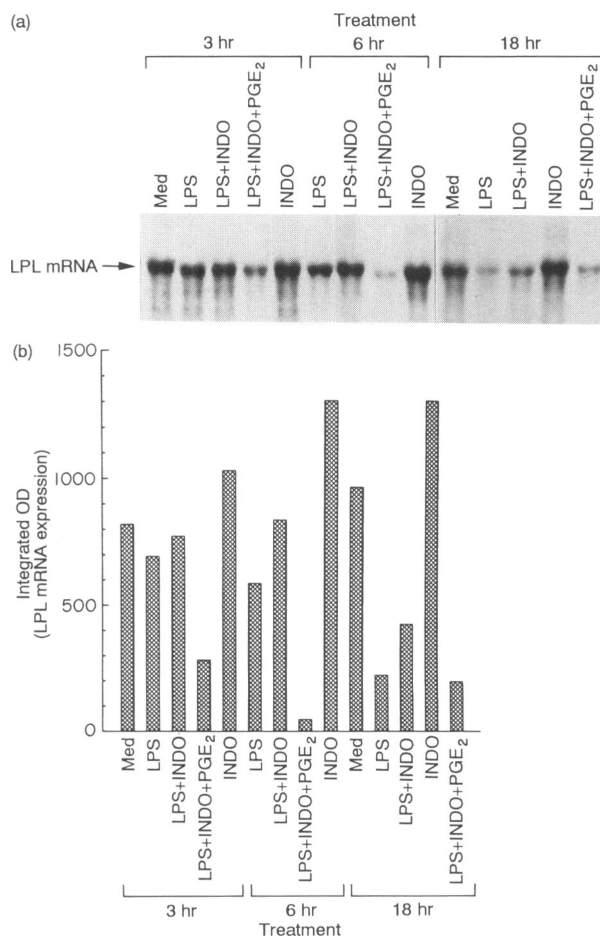

Figure 7. Effect of indomethacin on LPL mRNA expression. Peritoneal macrophages (10^6 cells/ml) were cultured in medium alone (Med) or in medium containing 1 μg/ml of LPS, 100 nM INDO, LPS plus INDO or LPS plus INDO plus 35 ng/ml of PGE_2. Total RNA were extracted after 3, 6 and 18 hr of culture and analysed by Northern blots for LPL mRNA expression (a) and then the expression of LPL mRNA was quantified by densitometric analysis of the autoradiograms obtained and OD values for LPL mRNA expression were normalized to the levels of β-actin mRNA expression in the same experimental sample (b).

(control) or in medium containing 1 μg/ml LPS, 100 nM INDO, LPS plus INDO or LPS plus INDO plus PGE_2 (35 ng/ml). The cultures were tested for the secretion of LPL protein, and for LPL enzymatic activity and mRNA expression.

As shown in Fig. 6a, LPL protein content was decreased threefold when macrophages were treated with LPS for 18 hr. The addition of 100 nM INDO reversed the inhibitory effects of LPS on LPL protein secretion. The addition of PGE_2 to LPS plus INDO led to a dramatic decrease in the LPL protein secretion. As shown in Fig. 6b, similar effects of INDO addition were observed when the activity of LPL was assessed. INDO alone did not affect either LPL protein levels or LPL enzymatic activity. As shown in Fig. 7a, when LPL mRNA expression was tested in the same cultures. β-Actin mRNA levels were not affected by the treatments (data not shown). The expression of LPL mRNA was quantified by densitometric analysis of the autoradiograms obtained, and optical density (OD) values for LPL mRNA expression were normalized to the levels of β-Actin mRNA expression in the same experimental sample (shown in

Fig. 7b). The addition of INDO resulted in some augmentation of LPL mRNA expression in LPS-treated cells, but did not fully reverse the inhibitory effect of LPS at any time-point tested.

Overall these results show that the decreased secretion of LPL protein and its activity in LPS-treated macrophages could be almost fully restored by treatment of the cells with INDO. In contrast, the inhibition of LPL mRNA expression induced by LPS was only partially reversed by INDO, indicating that multiple mechanisms are responsible for the down-regulation of LPL mRNA expression seen under these conditions.

DISCUSSION

Prostaglandins are synthesized by a variety of activated cell types during the course of arachidonic acid metabolism, through the cyclo-oxygenase pathway. Macrophages are an important source of PGE_2, which has been shown to play a critical role in modulating host immune responses. Underlining its importance in immune response modulation is the finding that PGE_2 has been implicated as a feedback inhibitor of interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α) production.[14–16]

LPL gene expression is differentially regulated in adipose tissue and macrophages. In fact, the treatment of adipose cells with TNF-α caused a marked decrease in LPL gene expression,[17] but did not affect LPL gene expression in macrophages.[12,13] Since macrophages are producers of LPL and PGE_2, it was important to determine whether or not PGE_2 affected LPL gene expression in these cells. We found, in fact, that exposure of murine macrophages to PGE_2 caused a significant decrease in the secretion of LPL and in the expression of LPL mRNA, suggesting that PGE_2 may down-regulate the expression of the LPL gene at the mRNA level.

In human adipose tissue two LPL mRNA species were detected, one estimated at 3·3 kb and the other at 3·8 kb.[18] Kirchgessner *et al.*[19] observed mRNA species of 1·7, 3·4 and 3·6 kb in mouse heart tissue and 3·4 and 3·6 kb in mouse adipose tissue. These differences in apparent size have been attributed to different polyadenylation signals.[19] We have observed that murine macrophages preferentially express the LPL mRNA of 3·6 kb, indicating that one polyadenylation site may be preferentially utilized by murine macrophages.

In adipose tissue, PGE_2 causes a significant increase in cAMP levels.[20] Kather & Simon[20] demonstrated that this increase in cAMP levels may be responsible for LPL gene down-regulation in adipose tissue. Furthermore, Gardette *et al.*[21] have shown that agents that increase cAMP levels diminished the secretion of the enzyme in macrophages. These findings prompted us to measure the levels of cAMP in macrophages exposed to PGE_2. We found an increase in cAMP levels of about threefold in macrophages treated with PGE_2. When the effect of cAMP on LPL gene expression was tested directly, we found that LPL activity decreased two- to fourfold following the treatment with cAMP. LPL mRNA expression was significantly inhibited as well. Overall, these data indicate that LPL gene expression is strongly down-regulated by exposure of macrophages to cAMP.

Humes *et al.*[7] demonstrated that macrophages synthesize and release prostaglandins in response to inflammatory stimuli. To estimate the levels and kinetics of prostaglandins secretion in our experimental system, macrophages were exposed to LPS for 3–18 hr and PGE_2 was measured. As shown in Fig. 4, increasing amounts of PGE_2 were secreted following LPS treatment. Other prostaglandins species (PGD_2, $PGF_{1\alpha}$, etc.) are secreted by macrophages in response to LPS as well, and they may also contribute to the inhibitory effect of LPS on LPL expression.

We observed that LPL protein content was decreased about threefold when macrophages were treated with LPS for 18 hr. Since it had been shown that treatment of macrophages with LPS inhibited LPL gene expression,[12,13] we have used INDO to test the possible involvement of secreted prostaglandins in the observed phenomena. The combination of 100 nM INDO with LPS decreased the inhibitory effect of LPS on LPL protein secretion. Similar effects of INDO addition were observed when LPL enzymatic activity was measured. Overall, these results indicate that the inhibition of LPL secretion could be restored by the addition of INDO. Since INDO addition to LPS had little effect on LPL mRNA level (a wide range of INDO doses was tested, 1 nM–1 μM; data not shown), the induction of LPL protein by INDO in LPS-treated macrophages was clearly proceeded by mechanisms other than modulation of mRNA expression. Conversely, the inhibition of LPL mRNA by LPS involved INDO-resistant mechanisms, as has been observed in the case of c-fms, another gene constitutively expressed at high levels in macrophages which can be inhibited by LPS.[22]

Semenkovitch *et al.*[23] and Doolittle *et al.*[24] have shown that post-transcriptional and post-translational mechanisms play an important role in the regulation of LPL gene expression in the 3T3 L-1 cell line, and a similarly complex mechanism may be involved in the regulation of LPL gene expression in LPS-activated macrophages. In fact, post-transcriptional control of gene expression in macrophages has been reported previously in the case of ribosomal gene expression, c-myc, c-fos, IL-1α, granulocyte–macrophage colony-stimulating factor, TNF-α and IL-1β gene expression.[25–30]

Overall our results demonstrate that PGE_2 is a potent inhibitor of LPL gene expression, and that its action may contribute to, but not fully account for, the inhibitory effects of LPS on LPL gene expression.

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